IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. 10/677,733	Customer No.: 23379
Applicant: Gardner et al.	Confirmation No. 4887
Filed: Oct 01, 2003	Group Art Unit: 1656
Docket No. UTSD:1510	Examiner: Nashed, Nashaat T.

Title: NMR Detection of Foreign PAS Domain Ligands

DECLARATION UNDER 37CFR1.132

I, Professor Stephen R. Sprang, declare and state as follows:

1. I am a Professor in the Division of Biological Sciences at the University of Montana, and Director of the Center for Biomolecular Structure and Dynamics located there. The Board of Regents of the University of Texas System is the assignee of this patent application. I have authored numerous scientific papers in the field of protein structure and regulation. I have read and considered this patent application, the Decision dated Sept 19, 2007, and the cited references.

2. Prior descriptions (including Fesik, WO97/18471) of "SAR by NMR" wherein structure-activity-relationships are obtained by NMR, have invariably targeted "druggable" proteins, apo-proteins structurally characterized to have preformed ligand binding pockets, proteins such as FKBP, stromelysin, E2 DNA binding domain, Erm methyltransferase, SH2 domains, etc.

3. In contrast, the recited PAS domains are determined to be absent any ligand binding pocket, and such proteins have not been, and would not have been screened for ligand binding by NMR because based on their structure. Further, these domains do not require protein chaperones or other cellular components to adopt a stable fold, nor do they have known ligands. Finally, PAS domains are involved in protein/protein interactions (PPIs), making them members of a class of targets that are widely considered "undruggable": see; e.g. Whitty et al. Nature Chemical Biology 2, 112-118 (2006), p.112, first para.

4. In view of this prior knowledge and experience, one skilled in the art would not have determined that a candidate target protein in fact has no NMR apparent ligand binding site, and then turned around and initiated an NMR-based screen of that very target for ligand binding.

5. As explained in our Specification some members of the PAS family are known to contain small molecule cofactors within their cores, and these cofactors are reportedly required for proper folding and functioning of the PAS domain within the context of the holo-protein.

Specification, p.1, line 22 - p.2, line 1. However, for most PAS domains there is no evidence for such a cofactor. In fact, structurally characterized PAS domains without bound cofactors (Amezcua et al., 2002; Erbel et al., 2003; Morais Cabral et al., 1998) show tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site. Specification, p.2, lines 2-5.

6. Since the prior work provided no evidence of cofactors for most PAS domains, and taught that those limited PAS domains having cofactors required them for proper folding, and taught that PAS domains without cofactors had tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site, one skilled in the art would not have suspected that such PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding; in fact, the prior art teaches squarely away from such use.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application and any patent issuing therefrom.

Date: November 19, 2007

Professor Stephen R. Sprang